50897001197

TI: L. Randecker HERD Disposition: 6/21/89

RG Host

RISK ASSESSMENT: PMN 89-632

[redacted]

[redacted]

I. BACKGROUND

[redacted], plans to import PMN substance 89-632, at a maximum production volume of [redacted] kg/yr [redacted] see Standard Review Engineering/Economics Reports for this case), for use as a light stabilizer for thermoplastics. It can be added to master batches or concentrates at concentrations of [redacted] or it can be added to finished products prior to forming operations at concentrations of [redacted]

Concerns are for immunotoxicity; effects on the liver, gastrointestinal tract, and blood; and developmental/reproductive system toxicity based on test data on hindered amine analogues.

The PMN substance is a solid with a M_n of 2,[redacted] there are no species having a MW of <500, and only [redacted] of the species have a MW of <1,000. The water solubility of the substance is <0.01 g/L (estimated), vapor pressure <1 x 10^{-6} torr at 25° C (estimated), and amine equivalent weight 266.

Test Data Provided in PMN. The submitter provided acute toxicity data showing that the rat oral LD_{50} of the substance is >3.2 g/kg, that the substance is nonirritating to rabbit skin at a concentration of 0.5 g, but that it is corrosive to rabbit eyes (unwashed) at a concentration of 0.1 g. The substance was also negative in an Ames assay in the absence and presence of metabolic activation up to a concentration of 100 ug/plate. At higher doses the substance was toxic to the test system.

[redacted]

II. CONCLUSIONS

Based on test data on the substance itself, it is concluded that it is a severe eye irritant. Based on test data on hindered amine analogues, it is concluded that the PMN substance poses a risk of immunotoxicity; toxicity to the liver, gastrointestinal tract, and blood; and reproductive system toxicity. Based on data from a range-finding study on another hindered amine analogue, the PMN substance may be developmentally toxic, but the data do not allow an estimation of risk.

See page 8 for risk calculations.

III. RATIONALE

Exposure

o Manufacture. In the absence of protective equipment, [redacted] workers at [redacted] could be exposed to a maximum of [redacted] mg/day by inhalation and to a maximum of [redacted] mg/day by the dermal route.

o Processing. In the absence of protective equipment, [redacted] workers (total) at up to [redacted] could be exposed to a maximum of [redacted] mg/day by inhalation and to a maximum of [redacted] mg/day by the dermal route.

o Use. No exposure to workers by any route is expected because the PMN substance will be encapsulated in a polymer matrix.

Absorption (taken from assessment for related case [redacted]

o Fractions of the PMN substance with a MW of >500 are not expected to be absorbed via the skin. Therefore, in the risk calculations, dermal exposure was discounted.

o If the substance, upon inhalation, is deposited as a dust in the upper respiratory tract, it is expected to be cleared by the mucociliary escalator and swallowed. Thereupon, it is expected to be absorbed via the gastrointestinal tract.

o Dust that reaches the alveolar regions of the lung may be phagocytized by alveolar macrophages and transported to the mucociliary escalator or absorbed as it is dissolved in pulmonary surfactants. The rate at which the respired concentration is eventually absorbed is expected to be slow. According to Dr. Leonard Keifer (Absorption/Metabolism expert, HERD), a reasonable approximation of this rate would be obtained by assuming that 50% of the inhalation exposure concentration is absorbed by the lungs.

Immunotoxicity

o The PMN substance is expected to pose a risk of immunotoxicity

to exposed workers based on test data on two hindered amine analogues.

Analogue 1: [redacted]

[redacted]

o A complete assessment of the data on [redacted] can be found in the HERD Risk Assessment Document for PMN [redacted]

o Two 90-day oral toxicity studies of [redacted] were conducted in rats (see table that follows on page 4). The submitter of these studies concluded that 0.01% is the NOAEL (no-observable-adverse-effect level) for [redacted]. However, the occurrence of lesions in the mesenteric lymph nodes and spleen (which appear to be treatment related) at the 0.01% dose makes this conclusion questionable. The 0.01% dose, equal to 6.6 mg/kg/day (average of 6.3 mg/kg in males and 6.9 mg/kg in females), would be more appropriate as a LOAEL (lowest observed adverse-effect level).

Analogue 2: [redacted]

[redacted]

o A complete assessment of the data on [redacted] can be found in the HERD Risk Assessment Document for [redacted]

Table. Results of Two 90-Day Oral Toxicity Studies of [redacted] in Male and Female Rats

Major effects noted	Dietary dose levels, Study I[a]				Dietary dose levels, Study II[b]				
	0%	0.1%	0.3%	1.0%	0%	0.01%	0.03%	0.1%	0.3%
Increase in WBC, lymphocyte, neutrophil levels	—	+ (f)	+*(m,f)	+*(m,f)	—	— (m) + (f)	— —	+ (m,f)	+ (m,f)
Decrease in relative liver weight	—	+*(m)	+*(m)	+*(m)	NR[c]	NR	NR	NR	NR
Increase in relative spleen weight	— —	— —	+ (m) +*(f)	+*(m) +*(f)	—	—	—	—	+ (m,f)
Lesions of the spleen	—	+ (m,f)	+*(m,f)	+*(m,f)	—	+ (m,f)	+ (m,f)	+*(m) + (f)	+*(m) +*(f)
Lesions of mesenteric lymph nodes	—	+*(m) + (f)	+*(m,f)	+*(m,f)	—	+ (m,f)	+*(m) + (f)	+*(m,f)	+*(m,f)
Focal necrosis and/or granuloma formation in mesenteric lymph nodes	—	—	+ (m,f)	+*(m) + (f)	—	—	—	—	+ (m,f)

[a] Levels correspond to 0, 67, 207, and 741 mg/kg/day for males and 0, 71, 220, and 733 mg/kg/day for females.

[b] Levels correspond to 0, 6.3, 18.9, 63.0, and 188.2 mg/kg/day for males and 0, 6.9, 21.5, 70.0, and 212.1 for females.

[c] NR = Not reported.

* - statistically significant.

000213

o Based on a 28-day oral subchronic study and two 14-day dermal studies on [redacted] the PMN substance may produce adverse effects to the immune system that could lead to serious health consequences such as immunodeficiency disorders or autoimmune diseases.

o In the 28-day oral toxicity study in rats, [redacted] produced changes in the lymphoreticular system involving the thymus, spleen, lymph nodes, and circulating white blood cells. There was also a depletion of circulating lymphocytes, which is indicative of immunosuppression. This observation is consistent with the finding that thymic tissue, the source of T-lymphocytes, showed moderate or marked atrophy in the 100-mg/kg and higher dosage groups.

o In both 14-day dermal studies in mice, [redacted] produced changes in the lymphoreticular system, as manifested by an increase in thymus weight, an increase in spleen weight and spleen cell number, and an increase in polymorphonuclear leukocytes and lymphocytes, all in a dose-related manner. Doses that were applied to nonabraded or abraded skin were 0.7, 7, or 70 mg/kg/day.

o Four immune function tests were performed in parallel with the standard dermal studies to provide more sensitive indicators of adverse effects on the immune system. The results showed that both cell-mediated and humoral immune responses were altered in mice exposed to [redacted] indicating that this compound and, by analogy, the PMN substance, has the potential for modifying immune responses. The LOAEL in these immune assays was 7 mg/kg/day.

Other Chronic Effects (Blood System, Liver, GI Tract)

o Data on the analogue [redacted] taken from a 28-day oral study in rats, indicate that the PMN substance may cause toxicity to the liver, GI tract, and blood system.

o In the 28-day study, [redacted] was given by gavage to male and female rats at doses of 60, 100, 300, 600, or 1,000 mg/kg/day.

o Blood System. Rats in the 300-mg/kg group showed leukocytosis, lymphopenia, and a marked prolongation of prothrombin time. Hematocrit values of animals in the 100-mg/kg group were decreased but the number of leukocytes was increased. The 60-mg/kg group also showed a slight but significant change in differential white blood cell count.

o Liver. The prolongation of clotting time may have resulted from impaired liver function. Other evidence that suggests liver damage includes increase of liver enzymes in the blood in the 100-mg/kg group. Upon autopsy, livers of animals in the 60- and 100-mg/kg groups showed soft yellow areas or small abscesses.

o Gastrointestinal Tract. Most rats in the 100-mg/kg group showed mucosal erosions and ulcers in the glandular part of the stomach. Because of acute congestion of the lung, spleen, and liver or advanced autolysis, autopsy and histological examination were not performed in the high-dose groups, whose members died during the test period.

o Although the study is of limited duration (28 days), the apparent LOAEL is 60 mg/kg.

Reproductive System Effects

o As for immunotoxicity and other chronic effects, the full assessment of the data on [redacted] can be found in PMN [redacted].

o The PMN substance may pose a risk of reproductive system effects to exposed workers based on test data on [redacted]. The analogue produced impaired spermatogenesis in rats fed 300, 600, or 1,000 mg/kg for 28 days. The LOAEL for this study is 300 mg/kg.

Developmental Toxicity

Analogue 3: [redacted]

o A dose-range-finding study of a hindered amine analogue for an upcoming two-generation reproductive system effects study in rats was submitted under section 8(e) of TSCA (see attached assessment by Dr. Seed).

o The exposure levels were 100, 500, 2,000, and 10,000 ppm of diet.

o Developmental toxicity (intrauterine death, decreased pup survival, decreased weight gain, delayed physical maturation) was evident at exposure levels of 2,000 and 10,000 ppm (ca. 164 and 786 mg/kg/day).

o There was paternal toxicity (reduced body weight gain, spleen and liver toxicity) at 500, 2,000, and 10,000 ppm ((ca. 32, 137, and 536 mg/kg/day) and maternal toxicity (reduced body weight gain, spleen toxicity at 10,000 ppm (ca. 786 mg/kg/day).

IV. SUBSTITUTES

V. TEST RECOMMENDATIONS

Because of high concern for the potential immunotoxicity and other chronic toxicity of the PMN substance, it is recommended that a 90-day oral (gavage) toxicity study be conducted, with special emphasis to be placed on the hematology, lymphoid organ weights (spleen, thymus), and histology as well as the cellularity of the bone marrow, thymus, and spleen. The study should also include a well-conducted histopathologic examination of the testes plus staging of sperm to address the concern for reproductive system effects. If immunopathology is observed, more comprehensive testing according to the National Toxicology Program's Immunotoxicology Tier II Screening Panel may be needed to further characterize immune alterations following exposure to the PMN substance.

Risk Calculations

I. Estimation of absorbed dose:
   a. No absorption via dermal route (see p. 2)
   b. Only 50% of inhalation exposure concentrations expected to be absorbed
   c. Mfg & proc. workers are exposed to a max. of 150 mg/day by inhalation; 50% of that is 75 mg/day. Divide this amount by 60 kg (human weight) to obtain a daily absorbed dose of 1.25 mg/kg/day.

II. Margins of Exposure for Immunotoxicity:
   NOAEL for analogue Chimassint 944 is 0.66 mg/kg/day
   (One-tenth the LOAEL of 6.6 mg/kg/day)

   [redacted] = No MOE

III. MOE's for liver, GI tract, blood system effects:
   NOAEL for analogue Tinuvin 144 is 6 mg/kg/day
   (One-tenth the LOAEL of 60 mg/kg/day)

   [redacted] 5

IV. MOE's for reproductive system effects:
   NOAEL for analogue Tinuvin 144 is 30 mg/kg/day
   (One-tenth the LOAEL of 300 mg/kg/day)

   [redacted] 24

8